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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/783,259	02/20/2004	Kenichiro Hasumi	358690-00005-1	7322

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/783,259	HASUMI ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *3-5,7,8 and 12-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6 and 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Response to Arguments

This Non-Final Office Action is in response to the After-Non-Final amendment filed on 19 May 2006. Claims 1-15 are pending, of which claims 1, 2, 6, and 9-11 are under examination and claims 3-5, 7, 8, and 12-15 are withdrawn from consideration.

Restriction of claims 12-15

Applicants' traversal to the restriction of claims 12-15 is acknowledged, however, not persuasive. Applicants' argument did not present any issues that materially affect the rationale for the restriction in the prior Office Action. Therefore, the restriction remains final.

Claim Rejections - 35 USC § 112, 1st ¶, enablement

The rejection of claims 1 and 6 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement, **is maintained** for reasons of record and extended to the dependent claims. Applicants' arguments have been fully considered but are deemed unpersuasive.

The breadth of the claim limitation "lymphocyte conditioned medium" (LCM) is so broad that it encompasses *all* chemokines and cytokines present in T cell culture medium from *any* mammal and *all* methods of T cell activation. Applicant' specification only refers to one embodiment wherein the adjuvant is based on a mixture of cytokines and chemokines derived from supernatant collected from cultured human peripheral blood mononuclear cells (PBMC) stimulated *in vitro* with antiCD3/CD28-coated beads.

This embodiment is not commensurate with the entire scope of the claimed invention. Therefore, there is at least a scope of enablement issue with the specification.

Applicants' citation of MPEP 2164.02 and *In re Brana*, 51 F.3d 1560, does not apply to the instant application. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art [emphasis added]. In the instant case, the only working example in the specification does not correlate to the claimed *in vivo* LCM immunotherapy in mammals based on the teachings in the art. The state of *in vivo* T-cell based therapy is highly unpredictable and awaits further development, as cautioned by Yee (2005), "The cytokines necessary for augmentation and maintenance of the immune effector function and survival, the costimulatory factors required, and the regulatory and inhibitory mechanisms that must be overcome to achieve tumor eradication must be addressed whether vaccine strategies or adoptive T cell therapy is used. However, the behavior and ultimate fate of effectors generated *in vivo* can be substantially different from those generated *in vitro*. It would be naïve to assume that *in vivo* conditions could be reproduced completely by manipulating conditions in vitro and there may be effectors of desired phenotype and function that can only be generated or more easily generated *in vivo* than *in vitro*. On the other hand, when effectors can be generated *in vitro*, their specificity, magnitude, surface and functional phenotype can be far better defined than those generated following *in vivo* immunization... it would be

presumptuous to believe that immune monitoring can characterize induced vaccine-elicited effectors to the same degree as effectors elicited *ex vivo*. Although there is no guarantee that infused T cells will behave *in vivo* in the same manner as one would be able to predict *in vitro*" (p.17). Yee further concludes, "Advances in this field will require judicious, step-wise translation of promising pre-clinical strategies into carefully designed clinical trials with discrete immunologic endpoints...The implementation of adoptive therapy however belies its experimentalistic origins: in cases where a population of T cells of desired magnitude with defined phenotypic and functional properties is required, for example, to validate findings arising from vaccine studies or provide proof of principle for hypotheses based on pre-clinical studies, this represents the optimal strategy" (p.24, last paragraph). Therefore, the claimed method of enhancing an immune response to an antigen in a mammal comprising administering LCM as an adjuvant for the antigen does not correlate with the *in vitro* antigen stimulation of human PBMC in the working example. Due to the high level of unpredictability in the state of the art (see references cited *supra*), the limited guidance on how to prepare LCM and the cytokine and chemokine analysis of LCM in the specification has left one skilled in the art undue experimentation of *in vivo* antigen stimulation with or without the LCM and with a different adjuvant to observe the adjuvant effect of LCM.

Applicants assert that a lack of clinical efficacy of the LCM is a requirement for obtaining approval from the FDA rather than obtaining a patent the Patent Office. The clinical efficacy is important to demonstration the correlation between *in vitro* and *in vivo*

results. Extrapolation from *in vitro* experimentation to *in vivo* administration of the LCM in mammals, especially in humans, is highly unpredictable in the state of the art due to the complex nature of immunology, see references above.

The claimed LCM adjuvant immunotherapy is not a routine practice in the art. Therefore, based on the evidence as a whole and the analysis of the *In re Wands* factors (A)-(H), the instant invention lacks an enabling disclosure for the entire scope of the claimed invention. See MPEP §2164.01(a) for the list of factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

Claim Rejections - 35 USC § 102

The rejection of claim 1 under 35 U.S.C. §102(b) as being anticipated by Baxevanis *et al.* (1999) **is withdrawn** in view of the Applicants' statement that Baxevanis does not teach administering LCM with an antigen.

Claim Rejections - 35 USC § 103

The rejection of claims 1 and 2 under 35 U.S.C. §103 (as) as being obvious over Baxevanis *et al.* (1997) in view of Santamaria *et al.* (1990) **is withdrawn** in view of Applicants' statement that neither reference discloses anti-CD28 coating on the beads.

The rejection of claims 1 and 9-11 under 35 U.S.C. §103 (as) as being obvious over Baxevanis *et al.* (1997) in view of Setaluri *et al.* (US 2002/0192727) **is maintained**

for reasons of record. Applicants' assertion of nonobviousness is not persuasive absent compelling reasoning.

New Claim Rejections - 35 USC § 112, 2nd ¶

Claims 1 and 2 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

In claim 1, the term "lymphocyte-conditioned medium" is indefinite because it is not clear to one skilled in the art what the active ingredient in the medium that acts as an adjuvant and what is the "condition" for the process of making this medium.

In claim 2, the term "anti CD3/CD28" is confusing because it can be interpreted as "CD3 and CD28" or as "CD3 or CD28."

New Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 2, and 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baxevanis *et al.* (1997) in view of Setaluri *et al.* (US 2002/0192727) and Mengozzi *et al.* (2001).

The instant claims read on a method of enhancing an immune response to an antigen in a mammal comprising administering LCM, which can be the PBMC of the mammal, in combination with an antigen.

Baxevanis *et al.* describe a method of adding supernatants collected from donor-derived PBMC stimulated with anti-CD3 monoclonal antibody.

Baxevanis *et al.* do not describe anti-CD3/CD28-coated beads for T cell activation and are silent on the antigen to be administered with the activated PBMC supernatant.

Setaluri *et al.* describe the dosage calculation and the administration of a tumor antigen hourly, daily, weekly, monthly, or yearly, by intramuscular or intravenous injection. See column 10, ¶90 and 92.

Mengozzi *et al.* suggest the anti-CD3/CD28-coated beads for *ex vivo* stimulation of T cells.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Baxevanis *et al.* by activation with anti-CD3/CD28-coated beads, as taught by Mengozzi *et al.*, and by combining with a tumor antigen and adapting the dosage calculation, administration route and schedule taught by Setaluri *et al.* The skilled artisan would have been motivated to do so to increase the efficiency of activation of T cell and the immunogenicity of the tumor antigen, by enhancing NK cell-mediated cytotoxicity, and activating the up-regulation of IL-2-specific receptor, cytokine synthesis and secretion, cell proliferation and acquisition of both antigen-specific and antigen-non-specific T-lymphocyte cytotoxicity. There would have been a reasonable expectation of success, given the *ex vivo* expansion of even HIV-infected T cells after anti-CD3/CD28 stimulation, as taught by Mengozzi *et al.* and the standard pharmaceutical procedures for administration of an anti-tumor antigen, as

taught by Setaluri *et al.* Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Contact Information

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
1 August 2006

8/1/06